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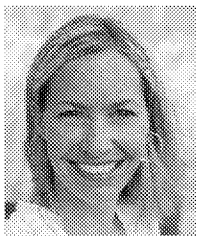
INSIGHT: New Approaches to Chemical Assessment – a Progress Report





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New Approach Methodologies (NAMs) for chemical hazard, exposure, and risk assessment are emerging tools that have the potential to increase the throughput of chemicals testing through analytical assays and bring robustness and mechanistic knowledge to chemical assessment. Recent advances in the development and application of NAMs in various research and regulatory contexts has set the stage for a transformation in toxicology that the U.S. National Academy of Science envisioned more than a decade ago.

Fast and Protective But before they can be formally adopted for use in risk assessment, we need to ensure that New Approach Methodologies will provide appropriate protection levels for human health and the environment.

Adopting these new approaches in chemicals regulation requires at least three essential elements: a solid scientific foundation demonstrating their robustness, validity, and general availability; public confidence in their ability to ensure protection of human health and the environment; and policy adoptions by national regulatory bodies that will enable chemical industry compliance. While there has been significant movement by regulatory agencies in this later regard (e.g., European Chemicals Agency, U.S. EPA, and Health Canada), coordination on the international level will be critical to ensuring barriers to adoption will be kept to a minimum.

One important effort to identify and overcome barriers to regulatory acceptance of NAMs is the Accelerating the Pace of Chemical Risk Assessment (APCRA) project, which began with a meeting of international regulatory agencies that the U.S. EPA hosted in 2016, with a follow up in Helsinki in 2017 that the European Chemicals Agency (ECHA) hosted. Building on the success of those two meetings, Health Canada hosted the third meeting in October 2018 in Ottawa. The main objectives of the Ottawa meeting were to review progress on a number of case studies that were specifically developed during the previous two meetings to build confidence in NAM application, expand the portfolio of case studies to include ecotoxicological examples, and discuss future directions of APCRA.

While attendance to the APCRA meetings has been limited to scientists from national regulatory agencies (many participants strongly feel this is one of the unique and valuable attributes of APCRA as it enables frank and open discussions), the Ottawa meeting included an open public session in which 120 attendees from academia, international and state governments, industry, and nongovernmental organizations participated via remote access. This session served as a key opportunity to share progress and findings to date with public stakeholders. Given the positive response to this session, the organizers are discussing further public outreach for the future.

Down to Cases In addition to a general overview of the Accelerating the Pace of Chemical Risk Assessment effort, the public session also included a presentation of three of the most advanced case studies.

The first case study, led by the U.S. EPA, is a retrospective comparison of whether in vitro bioactivity, as measured in ToxCast, can be used to derive a conservative point of departure (POD) for prioritizing and screening level risk assessments.

Comparisons are being made between PODs derived from traditional toxicology studies in animals with those from administered dose equivalent ToxCast responses for nearly 500 chemicals. Preliminary results show the mean POD_{NAM}/POD_{TRAD} ratio is 2.2 on a log scale (hence NAM-derived PODs are generally conservative by a factor of 100) and POD_{NAM} was greater than POD_{TRAD} for only 8 percent of the chemicals.

The case study is proceeding to explore a number of uncertainties in these comparisons and to extend the comparison of POD_{NAMs} with ExpoCast estimates, as well as exposure estimates derived for risk assessment as available, to provide bioactivity-exposure ratios. The early results suggest that NAM data provide a protective POD and could be used for risk-based prioritization and screening level assessments.

The second case study, led by ECHA, is similar to and builds on the first in objective, but does so in a prospective manner in determining whether the outcome from a refined in vitro assay battery could be used to derive a conservative point of departure and qualitative hazard indicator comparable to the outcome of a 90-day, repeat-dose toxicity study.

Still early in its formation (the study is projected to (liver and kidney) in parallel with a five-day in vivo transcriptomics study similar to that being evaluated by the U.S. NTP. The project will conclude with a qualitative and quantitative comparison of the three data streams. These comparisons are anticipated to inform the implementation of NAMs in tiered hazard assessments and to evaluate performance in various regulatory applications relative to traditional methods.

The U.S. EPA led the final case study presented in the public session and centered on evaluating high-throughput methods for estimating chemical exposures. It involved comparing ExpoCast exposure predictions with traditional exposure estimates performed under the Canadian Chemicals Management Plan of more than 3,000 exposure estimates for about 700 chemicals.

This case study was divided into two phases; the first focused on examining the current exposure data landscape. The second phase, informed by the outcome of the first phase, is starting to address challenges derived from different model structures, purposes, populations, and metrics.

The preliminary results for those chemicals that could be most directly compared indicated that the upper confidence bounds of the high-throughput estimates were generally consistent with the exposure estimates using more traditional methods. This was especially true for those chemicals with environmental media exposures only; consumer related exposures were quite variable and personal care products were in between in terms of the relationships. Further consideration is being given to interpreting results for high-exposure percentiles and specific populations.

Together these three case studies provide tangible evidence of the value of the APCRA effort. Envisioned to address key barriers in regulatory adoption of NAMs, each involves scientists from at least two countries, each is working to integrate complex data streams into digestible lessons on the relative merits of NAMs versus traditional approaches, and each is a learning test bed for regulators grappling with the application of emerging science to support decision-making.

Turning to the second goal of the Ottawa meeting, participants engaged in broader discussion of NAMs in ecological risk assessment guided by presentations from Environment and Climate Change Canada, the U.S. EPA, and ECHA.

Some general observations were: (1) the tremendous complexity of ecosystems has contributed to limitations in NAM applications compared to human health; (2) modeling was more accepted in ecotoxicological assessments, if only because of the sheer number of species that need to be protected versus the limited number of species that are tested experimentally; and (3) molecular biomarkers measured using various "omic" technologies could offer an opportunity to detect key events in critical species that can be extrapolated based on conserved biological processes.

Two proposed case studies also were discussed, the first involving application of transcriptomic technology in zebrafish for predicting endocrine disruption and general toxicity, the second on estimating protective maximum acceptable toxicant concentrations for ecological species from bioactivity data.

Two other sessions of the meeting focused on approaches for building confidence in the use of New Approach Methodologies. The first was focused on challenges and outcomes resulting from establishing confidence in NAMs by comparing results with traditional toxicology methods including acute and repeat-dose testing in animals, as well as in vitro skin sensitization assays.

The second part dealt with integrating NAM data to enhance mechanistic understanding in overall weight-of-evidence processes. Highlights of this session included perspectives from the Organization for Economic Cooperation and Development on the application of Integrated Approaches to Testing and Assessment, outcomes from a recent National Academies workshop that explored how to build trust in New Approach Methodologies by analyzing their use in several different decision contexts, and the use of NAMs in the new Toxics Substance Control Act in the U.S. These all point to both the opportunities and challenges in adopting NAMs in decision-making.

More Ahead As the meeting closed, the participants reflected on the value of APCRA and its future. Based on progress in a number of case studies that originated specifically following discussions at previous meetings, it is clear that there is value in the APCRA process in bringing together regulatory scientists from throughout the world. Because these case studies were specifically designed to address issues in chemical assessment for regulatory agencies, the results are sure to have direct impact on the utilization of NAMs in chemical regulation internationally. It is highly unlikely the collaborative case studies would be developed in the manner in which they have evolved without APCRA discussions.

In this regard, the role of APCRA as an incubator for ideas and a think tank for moving forward is unique and should be maintained. Multiple participants stressed how they valued the closed nature of the meeting, which allowed frank discussions across the international community on strengths and weaknesses of NAMs, as well as traditional toxicological methods.

It also was recognized that this opportunity for candor needs to be balanced against transparency with the

larger scientific and public communities so that advancements for the application of NAMs in risk science can be shared and more broadly appreciated and accepted.

Based on the positive discussions, the U.S. EPA agreed to host the fourth meeting of APCRA in 2019, at which time some of the more advanced case studies are projected to have begun to publish their findings. Those publications will likely attract broad interest and an APCRA communication strategy will be an important component of that meeting.

Disclaimer: The views expressed are those of the authors and do not necessarily represent the policies of the U.S. Environmental Protection Agency, the European Chemicals Agency, or Health Canada.

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